DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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Food and Drug Administration
Center for Biologics Evaluation
and Research
1401 Rockville Pike
Rockville MD 20852-1448

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Warning Letter

Douglas C. Wolf, M.D.
Atlanta Gastroenterology Associates
5671 Peachtree Dunwoody Road, Suite 635
Atlanta, Georgia 30342

Dear Dr. Wolf:

During the two inspections that were conducted between January 29 and February 18, 2002 (the "first inspection"), and August 26 and September 13, 2002 (the "second inspection"), Ms. Stephanie E. Hubbard and Ms. Claudele Razo, investigators with the Food and Drug Administration (FDA), reviewed your conduct of the following five clinical studies.

1. **Study 1:**

2. **Study 2:**

3. **Study 3:**

4. **Study 4:** [redacted]

5. **Study 5:** [redacted]

These inspections were conducted under the FDA's Bioresearch Monitoring Program, which includes inspections designed to audit the conduct of clinical research involving investigational drugs. During the first inspection, Study 1 was audited, and during the second inspection, the FDA investigators conducted an audit of Studies 2 through 5. A Form FDA-483, Inspectional Observations, was issued to and discussed with you at the conclusion of each inspection. We received your response letters dated, respectively, February 20, 2002, (response 1), and November 13, 2002, (response 2) to the inspections. We reviewed the inspection reports, Forms FDA-483, and your responses.

We have determined that you violated regulations governing the proper conduct of clinical studies involving investigational new drugs, as published in Title 21, Code of Federal Regulations (CFR), Parts 50 and 312 (available at http://www.access.gpo.gov/nara/cfr/index.html). The applicable provisions of the CFR are cited for each violation listed below. Some of the violations were not cited on the Form FDA-483, but were evident from the documents that the FDA investigators collected during the inspections. To the extent applicable, this letter lists in brackets the Observation Numbers ("Obs. #") that correspond to the violations cited below.

1. **You failed to conduct an investigation according to the signed investigator statement, investigational plan, and protocol to protect the rights, safety, and welfare of the subjects under your care. [21 CFR § 312.60].**

   Study 1:

   A. You failed to follow the study protocol in administering the study drug according to the study schedule. 21 of the — subjects enrolled in the study received at least one study drug infusion not in accordance with the protocol-specified schedule during the maintenance phase. [first inspection, Obs. #2 (first example)]

      You explain, in response 1, the difficulty of adhering to the study visit schedules in a long-duration study protocol. However, both the protocol inclusion criteria for subjects and the consent forms approved by the

Institutional Review Board (IRB) stress that the success of the study required adhering to the study visit schedules and required the long study duration. For such studies, you must plan properly to ensure that the schedule requirements are met. We received the corrective action plans that you intend to implement in your future clinical studies, and we urge you to ensure that they are fully implemented and to verify that they are effective in ensuring that subjects adhere to the study visit schedules.

B. The protocol requires that study subjects be randomized to a treatment group at week— and be continued in the treatment group unless otherwise indicated by a loss of response. The following table illustrates that you failed to follow this protocol directive [first inspection, Obs. # 2 (second example)]:

Subject	Treatment assigned on week —	Treatment administered on study week
09003	Placebo	—mg/kg at week-—
09005	— mg/kg	—mg/kg at week-—
09006	Placebo	—mg/kg at week-— —mg/kg at week- —
09009	— mg/kg	—mg/kg at week-—
09011	Placebo	—mg/kg at week-—
09018	—mg/kg	No administration of study drug at week-—
09020	—mg/kg	—mg/kg at week-—

Your response 1 indicates that you were not aware of the deviations in study drug dosage and administration due to the blinded nature of the study randomizations. Nevertheless, as the clinical investigator, you are ultimately responsible for the pharmacy staff. We acknowledge your plan to institute intensive protocol training for the pharmacists in future studies, and recommend that you take steps to verify that the protocol training is effective.

C. The protocol requires the assessment of Crohn's Disease Activity Index (CDAI) at week—and week— for evaluating the response status at week-— to be randomized to one of the ——treatment groups. You failed to obtain the complete data for CDAI assessment. For subjects 09007, 09012, and 09018, on the week-—visits, no data from the subject's diary – a critical component used to calculate CDAI – were obtained. For subjects 09008 and 09020, for the week—assessment, data for hematocrit – another component of the CDAI calculation – were not obtained.

D. You did not ensure that the investigation is conducted according to the signed investigational plan and protocol as shown below.

i. The protocol requires that subjects be provided with diary cards on the pre-screening visit that need to be completed during the —— days before screening to determine eligibility to participate in the study. Your enrollment records indicate that subject 09025 was prescreened and screened on the same visit date, 12/9/99.

ii. The protocol requires that subjects qualifying for the study be enrolled within —days of the screening visit. You enrolled subjects 09009, 09010, 09011, 09019, and 09026 in the study outside of this time frame.

iii. The protocol requires the week—visit to be —weeks from week— visit with an acceptable visit window for the week—visit as ±— day. You did not follow this protocol requirement for nine subjects.

E. The study protocol requires the use of a standard weight table provided with the protocol for determining the standard weight that is used for the study subjects in the assessment of CDAI. You did not use this table for 13 subjects in the CDAI assessments on the screening and week —visits and for subject 09006 on the screening visit. [first inspection, Obs. #1.b]

In response 1, you acknowledge this oversight and explain that you corrected this deficiency after the sponsor monitor informed you. However, we note that you did not use the standard weight table provided with the protocol for 13 subjects after the sponsor monitor's correspondence to you dated 6/22/99 required you to use this standard weight table.

F. You enrolled subject 09018 in the study on 8/2/99 even though the subject's CDAI score, when correctly calculated, was 425 on the screening visit. The protocol requires a CDAI score between ——and —— for the subjects to participate in the study.

G. You failed to follow the investigational plan and administered an incorrect study drug to study subjects. The pharmacy records indicate that subjects 09021 and 09022, and 09024 did not receive the study drug intended for the current clinical study under investigation. Subjects 09021 and 09022 received a drug intended for another study on the crossover episodic treatment week and subject 09024 received the drug intended for another study on week-— of the study treatment period.

Study 2:

A. The investigational plan and protocol require that subjects who fulfill the eligibility criteria be stratified in to one of the two groups, based upon their current Crohn's disease medication, for further active study drug or control

drug allocation within that group: those subjects receiving ———— ————. or ————treatment at screening to be in one group and those not receiving any of these treatments to be in another group. Of the 5 subjects in the study, you failed to correctly stratify subjects 1051, 1052, and 1054, who were not receiving the listed treatments, and therefore should have been stratified into the second group. [second inspection, Obs. #1]

In response 2, you acknowledge the violation and propose corrective action plans in your future studies. We remind you that incorrect stratification of study subjects may lead to inaccurate efficacy analysis of the study drug in clinical trials.

B. You failed to follow the study protocol regarding steroid (prednisone) dosage prior to screening.

i. You enrolled subject 1051 on the study who did not meet the inclusion criterion regarding a stable prednisone dose prior to study entry and administered study drugs on 8/17/98 and 10/16/98. The study protocol dated 3/23/98 required subjects to be receiving —— ——mg. per day of prednisone for at least—weeks with a stable dose for at least—weeks prior to screening. The progress notes dated 7/7/98 and 8/5/98, signed by your sub-investigator, Dr. ———— , and the subject's medication record indicate that this subject was on prednisone tapering dosages and was on a—mg. dose on the above mentioned dates. This subject, screened on 8/5/98, did not meet the inclusion criteria of a ————mg. per day of prednisone for—weeks prior to screening nor was the subject on a stable prednisone dose for—weeks prior to screening.

ii. You failed to follow the protocol requiring subjects to receive prednisone dosage of————mg. per day for at least—weeks prior to screening for subject 1055. The progress note dated 11/19/98 for subject 1055 indicates that subject was on a prednisone dosage of— mg. per day that was not allowed by the protocol.

C. You failed to follow the study protocol requirement that Erythrocyte Sedimentation Rate (ESR) be measured for study subjects on———— weeks-———————— and———— visits during the blind treatment period. You failed to obtain, or incorrectly obtained, the ESR on at least one occasion for all subjects enrolled in the study. [second inspection, Obs. #7] In response 2, you acknowledge this deficiency and propose corrective action plans.

D. The study protocol requires that daily diary card data be recorded by all subjects from screening to week- — during the blind treatment period and

to week-— during the open label treatment period. The study schedule required that data collected from the subject's diary card over the —days prior to the visit be used in the calculation of subjects' CDAI score. You failed to collect the diary card data as required by the protocol for four (subjects 1051, 1052, 1053, and 1054) of —— subjects enrolled. [second inspection, Obs. # 12]

In response 2, you acknowledge the deficiency and provide corrective action plans implemented in other clinical studies. You explain that "the patient's diary is one aspect of research that is primarily the responsibility of the patient. It is often difficult to anticipate the lack of compliance by patients participating in a research protocol." We remind you that the study handbook indicated the importance of diary data and the importance of procedures to ensure compliance regarding collection of this data. Further, in obtaining the informed consent from subjects, the signed agreement by you or a sub-investigator indicates that the study procedures were explained to the subjects.

Study 3:

A. The sponsor provided you with a signature log to be completed by the study personnel participating in the study with the authorized function in the study and your authorization with signature and date. You failed to get the signature from the infusion nurse who infused the study drug on 8/7/01 to subject 0760, and on 8/7/01, 10/10/01, and 12/5/01 to subject 0761. Furthermore, you authorized her function on 3/12/02 after the infusions were completed.

B. You failed to assess both subjects as required by the protocol within the protocol allowed study visit schedules. Examples include, but are not limited to:

Subject	Protocol allowed schedule for visits	Actual study visit and assessment
0760	Week— ± —day	Week—visit on 8/7/01 and week-—on 8/17/01
0761	Week — ± —day	Week— on 8/7/01 and week— on 8/29/01
	Week— ± —days	Week—visit on 9/4/01 and week—on 10/10/01

C. You failed to follow the protocol regarding steroid dose increase to the pre-study dose level in the treatment of flare for subject 0760. The study protocol states that "if at any time a patient requires rescue therapy for a flare (CDAI——— they will have their steroid dose increased to the daily dose they were on at the entry into the study . . . ." The subject entered the study on 7/24/01, and was on a— mg. dose of steroid that was

tapered off completely by 9/12/01. A telephone contact with the subject's mother, dated 9/20/01, indicated that this subject was asked to stay on a — mg. dose of prednisone that this subject started taking on 9/17/01 because of a disease flare, rather than instruct the subject to take the entry level dose of — mg. prednisone. The episode was not documented as an exception, as the protocol required. [second inspection, Obs. # 21]

In response 2, you acknowledge the deficiency. We note that you also failed to measure the disease flare using the CDAI score for this subject on 9/25/01 during the week- —study drug infusion as required by the protocol.

Study 4:

A. You failed to follow the protocol requirement of adhering to the study visit schedules for subject 115 on at least three occasions. Examples include, but are not limited to:

i. Week— visit was conducted 24 hours after the study drug administration whereas the protocol requires the first follow-up visit to occur — days after the last dose of study drug administration.

ii. Week- — visit was not conducted until 11/8/01, whereas the week- — visit was on 10/25/01.

iii. Week- — assessments were delayed by a week and performed on 1/21/02 on week- —

B. You failed to follow the protocol requiring the measurement of ESR during the pre-treatment phase and on week- — of the treatment phase for subjects 010 and 115, respectively.

2. You failed to obtain informed consent from study subjects in accordance with the provisions of 21 CFR Part 50. [21 CFR § 312.60].

Study 1:

You failed to obtain the signed informed consent for the following subjects in the revised consent forms approved by the IRB on more than one occasion: Subjects 09002, 09003, 09007, 09009, 09011, 09018, 09019, 09020, 09022, 09025, 09025, 09026, 09027. [first inspection, Obs. # 3, and collected exhibits]

Studies 2 and 3:

A. For subject 1051 enrolled in Study2, you failed to obtain the written informed consent on the consent form approved by the IRB on 10/22/98. [second inspection, Obs. # 18]

B. For subjects 0760 and 0761 enrolled in Study3, you obtained the written informed consent using a consent form approved by the IRB on 1/17/01 but superceded by a consent form approved by the IRB on 3/21/01. [second inspection, Obs. ## 19 & 26]

In response 2, you acknowledge this deficiency, indicate your attempts to reach the subjects by certified mail and obtain the revised consent forms, and provide corrective action plans to be implemented to prevent the occurrence of this deficiency in your future studies.

3. **You failed to maintain adequate records of the disposition of the drug. [21 CFR § 312.62(a)].**

Study 2:

Your contract pharmacy failed to maintain adequate records for the disposition of the study drug. Study Drug Preparation Forms (SDPFs) could not be located for the week-—infusion during the blind treatment period for subject 1051 and for the week-— infusion during the open label treatment period for subject 1052. As SDPFs were the only pharmacy records that documented the study drug vials used in the preparation of study drug infusion with appropriate kit numbers and dosage, whether active or placebo, adequate records of week—infusion data for subjects 1051 and 1052 were not maintained.

In response 2, you propose corrective action plans to prevent the occurrence of this deficiency in your future clinical trials. Your plans, if successfully implemented, appear adequate.

4. **You failed to prepare and maintain adequate and accurate case histories . [21 CFR § 312.62(b)].**

Study 1:

Subjects' case histories include worksheets for entering study-related data from the subject's diary card and other assessments in order to obtain CDAI scores as required by the study flow chart in the protocol on scheduled study weeks. This worksheet provides the total CDAI score for that visit which is used in the study for assessing the clinical response status for that week in comparison with the baseline CDAI score. For 27 of—subjects, the case histories contain numerous unexplained data entry changes and/or errors in the calculation of the CDAI

values resulting in documentation deficiencies and discrepancies as shown in items 4A and 4B.

A. Data entered in the source documents were corrected without adequate recorded rationale for 26 of the— subjects, including but are not limited to: subjects' weight, data obtained from subjects' diaries, hematocrit value, and the value of abdominal mass.

B. For 24 of—subjects, the response status at week-— cannot be determined accurately as a result of documentation discrepancies in the CDAI values between the source records at week-—week-—and values reported by the———————————————— on the Enrollment Confirmation Form (ECF) or the Randomization Confirmation Form (RCF). Examples include, but are not limited to: (a) subjects 09001, 09003, 09005, 09009, 09010, 09012, 09013, 09014, 09015, 09018, 09020. 09021, 09022, and 09025 whose CDAI values at screening or week —from source records are discrepant from that reported on the ECF. [first inspection, Obs. #1.a and collected documents] (b) subjects 09001, 09002, 09006, 09009, 09014, 09020, 09022, 09025, and 09028 whose CDAI values recorded on the worksheet at the week— visit are discrepant from that reported by——— on the RCF. [first inspection, Obs. #1.a (last sentence) and collected documents]

Study 2:

For subject 1054, documents are discrepant regarding the oral contraceptive use and the reason for the withdrawal on 10/23/98 from the study.

A. The study protocol required the female subjects enrolled in the study to be on a combination of oral contraceptives and condom use during the study and for— months after the completion of the study. The inclusion/exclusion criteria during screening on 9/8/98 indicated the subject as not on any oral contraceptive but rather as surgically sterile as of 1994. This data was changed by the study coordinator on 1/5/99 to indicate that the subject was using oral contraceptives at screening, but that change is not supported by source documents. We note that the subject called the study coordinator on 1/5/99 to provide notice of the subject's pregnancy.

B. The progress notes and other source records for the subject's study visit on her week-4 visit following the study drug infusion, indicate the subject was having increased abdominal pain, intermittent nausea and vomiting, appearance of two buccal ulcers, and tongue plaque. The case report form (CRF) for that visit indicated the subject withdrew due to disease progression whereas the sponsor monitor's letter dated 1/7/99 noted the subject's withdrawal from the study after developing a rash. Your file note dated 8/23/02 indicated that the subject withdrew due to an infusion

reaction that was changed on 8/27/02 to withdrawal due to disease progression.

Study 3:

A. Documents are discrepant regarding the steroid, prednisone, administration to study subject 0760. Subject's concomitant medications CRF indicated that the subject was on prednisone dosage of — mg. per day starting on 9/17/01 that was not discontinued until 5/4/02, whereas the source documents indicated that this subject started prednisone dosage of —mg. per day on 10/02/01 that was tapered and discontinued on 10/31/01.

B. Documents are discrepant regarding subject withdrawals from the study. You reported to the IRB on 5/10/02 the withdrawal of subject 0761 from the study. However, subject 0760 withdrew from the study on 10/31/01 and you did not include that information in the above mentioned report to the IRB.

C. The study protocol required that the data for the CDAI be collected at weeks-———— and ————visits. You failed to collect or collected incomplete data for both subjects as shown in the following example: CDAI for subject 0760 on week— and ————visits and for subject 0761, on ———— and————visits.

Study 5:

A. Documents are discrepant for subject 558001 on the screening visit regarding stool culture. Even though a the laboratory source document indicates a test result for the stool culture taken on 4/26/02, neither the subject's screening visit progress notes dated 4/26/02 nor the study-exclusion-criteria CRF indicated that the stool culture was taken.

B. Study Drug Prescription Form provided by the sponsor does not contain any data regarding the study drug preparation such as date and time the infusion was prepared, and the pharmacist's signature and date for subject 558001 for the week-—infusion and for subject 558002 for the week— infusion.

C. For subject 558002, the CDAI assessment dated 7/1/02 for the week-— infusion contains an incorrect calculation for the question regarding anemia. Subtracting the subject's hematocrit value of 42% from the standard value for male should give a corrected CDAI score of 466 instead of 436.

D. There is no documentation of the protocol exemption from the sponsor for subject 558002 regarding the initiation of antibiotic use. Subject's

progress note dated 6/20/02 indicates that the sponsor monitor allowed the initiation of Flagyl and Cipro and the subject to remain on the study that was not supported by any document from the sponsor.

In your response letter dated 11/13/02, for Studies 2 and 3, you explain that many of the deficiencies were due to the former study coordinator's error and you indicate that the coordinators involved in the Crohn's disease studies are not involved in your clinical practice. We note that during the site initiation visit on 7/6/98 for Study 2, the sponsor monitor reviewed your obligations such as completing CRFs and monitoring conventions, investigator responsibilities including Form FDA 1572, and dispensing and administration of study drugs including randomization. You signed investigator agreements for Study 3 with the study sponsor on 8/3/00, 6/14/02, and 8/5/02 to conduct the trial according to the protocol and agreed to ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed about their obligations in meeting the commitments made in the investigator agreement. You were aware of your commitments and failed to adhere to them.

We note that you are involved in ——clinical trials including some of the above studies. We acknowledge your plan to obtain additional audits by sponsors and monitors as well as an audit of the contract pharmacy, and urge you to review all stages of your studies to ensure that you have implemented corrective action at every stage, including, but not limited to, pre-screening stages, where applicable.

This letter is not intended to be an all-inclusive list of deficiencies in your clinical studies of investigational drugs. It is your responsibility to ensure adherence to each requirement of the law and applicable regulations and to protect the rights, safety, and welfare of subjects under your care.

You should notify this office, in writing, within fifteen (15) business days of receipt of this letter, of the steps you have implemented and plan to implement to prevent the recurrence of similar violations in on-going and future studies and to assure that they are conducted in compliance with 21 CFR Parts 50 and 312. Any request for an extension of the 15 business days should provide a reasonable basis for such extension.

This Warning Letter is issued to you because of the serious nature of the observations noted at the time of the FDA inspections. Please be advised that the failure to effectively put into practice the corrective actions you plan to implement and/or the commission of other violations may result in the initiation of enforcement action(s) without further notice. These actions could include initiation of clinical investigator disqualification proceedings, which may render a clinical investigator ineligible to receive investigational new drugs, and/or injunction.

Please send your written response to:

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We request that you send a copy of your response to the FDA District Office listed below.

Sincerely,

Steven A. Masiello
Director
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Center for Biologics Evaluation and Research

cc:

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